IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Lorens et al.
Application No. 10/696,909
Filed: October 29, 2003
Confirmation No. 9257
For: MODULATORS OF ANGIOGENESIS AND TUMORIGENESIS
Examiner: Peter J. Reddig
Art Unit: 1642
Attorney Reference No. 7946-79836-01

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COMMISSIONER FOR PATENTS

REPLY BRIEF

This Reply Brief, filed in accordance with 37 C.F.R. § 41.41, responds to the Examiner's Answer dated May 10, 2011. A two-month period for response was set, making a reply due on or before **July 10, 2011**. This Reply Brief is considered to supplement the existing Appeal Brief filed by Appellants on March 3, 2011. All previous arguments presented in Appellants' Appeal Brief continue to be applicable and asserted in this Appeal.

Grounds of Rejection to be Reviewed on Appeal

Claims 1, 14-18, 27, 41-44, 54, and 55 are pending and are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Mor (U.S. Pat. Publication No. 2003/0157573) in view of Klinghoffer *et al.* (U.S. Pat. Publication No. 2004/0077574), further in view of O'Donnell *et al.* (*Am. J. Pathol.* 154:1171-1180, 1999), and further in view of Varner and Cheresh (*Curr. Opin. Cell Biol.* 8:724-730, 1996).

Reply to Examiner's Answer

In the Examiner's Answer, the Office maintains the rejection of claims 1, 14-18, 27, 41-44, 54, and 55 under 35 U.S.C. § 103(a) as allegedly unpatentable over Mor in view of Klinghoffer *et al.*, further in view of O'Donnell *et al.*, and further in view of Varner and Cheresh. The Office continues to assert that it would have been obvious to one of skill in the art to screen for inhibitors of Axl to identify angiogenesis inhibitors particularly in view of the disclosures of

Mor and O'Donnell *et al.* Appellants have previously argued that Mor and O'Donnell, alone or in combination, do not provide one of skill in the art with sufficient motivation to identify angiogenesis inhibitors by screening for Axl inhibitors, nor would one of skill in the art have had a reasonable expectation of success in doing so. Furthermore, Klinghoffer *et al.* and Varner and Cheresh do not provide any reasonable expectation that Axl is involved in angiogenesis and do not remedy the deficiencies of Mor and O'Donnell *et al.* Those arguments are reasserted herein.

No Motivation to Combine

The Office relies on the combination of Mor and O'Donnell *et al.* to provide motivation to one of skill in the art to identify inhibitors of angiogenesis by screening for inhibitors of Axl activity. Varner and Cheresh merely disclose that $\alpha v\beta 3$ integrin plays a role in angiogenesis and Klinghoffer *et al.* merely describe use of small interfering RNAs as modulators of cell signaling. Appellants re-emphasize that Mor merely makes a single conclusory statement that compounds identified by the assays disclosed in Mor could be used as "anti-angiogenic drugs for the treatment of cancer and other conditions where preventing or reducing *proliferation* of endothelial cells is desired" (Mor, paragraph [0090], emphasis added). Mor does not provide any evidence that Axl activity is related to angiogenesis. Rather, Mor discloses ubiquitous expression of Axl and specifically its role in fibrosis (*e.g.,* Mor, paragraphs [0240-0241] and [0249-0257] and).

In response to Appellants' previous argument that the overall teaching of Mor relates to cell proliferation, the Office states that Mor "is relevant for all it contains" (Examiner's Answer, page 15). Appellants' re-emphasize that the teachings of Mor must be considered as a whole. "All of the disclosures in a reference must be evaluated for what they fairly teach one of ordinary skill in the art…[W]hen 'all of the disclosures in a reference' are considered, the overall suggestion to emerge from the prior art reference may be contrary to that which might appear from an isolated portion of the reference." *In re Langer*, 465 F. 2d at 899, 175 USPQ at 171 (CCPA 1972). Thus, the single statement in paragraph [0090] cannot be isolated from Mor, but must be considered in the overall context of the document, which otherwise is entirely related to identifying inhibitors of fibrosis and nephropathy (*e.g.,* Mor, paragraphs [0033-0036]). Taken as a whole, "the overall suggestion" of Mor to one of skill in the art would be that inhibitors of cell

proliferation or fibrosis, *not* inhibitors of angiogenesis, could be identified by screening for inhibitors of Axl.

O'Donnell *et al.* describe the expression of Axl in synovial tissue from patients with rheumatoid arthritis and the role of the Axl ligand Gas6 in endothelial cell survival (*e.g.,* O'Donnell *et al.,* page 1175, col. 1 to page 1176, col. 2, top). O'Donnell *et al.* merely provide speculative statements about the role of Gas6 (which is an agonist for Axl, Sky, and Mer, not just Axl) in "nonmitogenic" processes in endothelial cells, such as cell adhesion (page 1177, col. 2, last paragraph to page 1178, col. 1). Thus, when read as a whole, "the overall suggestion" of O'Donnell *et al.* to one of skill in the art would be that inhibitors of apoptosis, *not* inhibitors of angiogenesis, could be identified by screening for inhibitors of Axl. Thus, even in combination, Mor and O'Donnell *et al.* are directed to endothelial cell proliferation and/or survival (not angiogenesis) and one of skill in the art would not be motivated to identify inhibitors of angiogenesis by screening for inhibitors of Axl.

Furthermore, in the Appeal Brief submitted on March 3, 2011, Appellants pointed out the parallels between O'Donnell *et al.* and Healy *et al.* (*Am. J. Physiol. Lung Cell Metabol.* 280:L1273-L1281, 2001). Healy *et al.* was previously relied on in a rejection under 35 U.S.C. § 103(a) (in combination with Varner and Cheresh and Klinghoffer *et al.*). The rejection over Healy *et al.* was reversed by the Board in the previous appeal of this application (BPAI Decision 2009-011194, March 16, 2010). Appellants recognize that the present rejection is not based on Healy *et al.*; however, the parallels between the disclosures of Healy *et al.* and O'Donnell *et al.* are relevant, particularly in light of the Board's reversal of the rejection based on Healy *et al.* Specifically, both O'Donnell *et al.* and Healy *et al.* disclose that Gas6 increased cell number and decreased apoptosis of endothelial cells expressing Axl. Healy *et al.* also disclose that apoptosis plays a role in vascular remodeling. The Board previously found that Healy *et al.* did not provide sufficient motivation for one of skill in the art to assay an angiogenesis marker such as $\alpha v\beta 3$ in endothelial cells (BPAI Decision 2009-011194, March 16, 2010, page 17, last paragraph). Similarly O'Donnell *et al.* include only speculative statements that Axl could possibly play a role in some cellular events associated with a number of processes, including possibly angiogenesis. This does not provide sufficient motivation for one of skill in the art to

consider that an Axl inhibitor would be an inhibitor of angiogenesis or to assay angiogenesis phenotypes in a cell-based assay, even in view of the disclosure of Mor (particularly when both Mor and O'Donnell *et al* are read as a whole, as discussed above).

No Reasonable Expectation of Success

Appellants re-emphasize that one of skill in the art would not have had a reasonable expectation that a screen for Axl inhibitors would successfully identify inhibitors of angiogenesis in view of Mor and O'Donnell *et al.* Both Mor and O'Donnell *et al.* disclose a potential role for Axl in cell proliferation and/or survival, events that are relevant to many cellular processes, not specifically angiogenesis. For example, Frater-Schroder *et al.* (*Proc. Natl. Acad. Sci.* USA 84:5277-5281, 1987) disclose that compounds that inhibit cell proliferation (even endothelial cell proliferation) are not predictably compounds that inhibit angiogenesis (*e.g.,* Frater-Schroder *et al.,* page 5277, col. 2, first full paragraph; page 5279, col. 2, last paragraph). Thus, there is no reasonable expectation that screening for inhibitors of Axl, which in view of the references is understood to play a role in endothelial cell proliferation, would successfully identify inhibitors of angiogenesis.

The Office states that Mor "clearly indicates that by screening for inhibitors of Axl kinase activity, which is expressed in endothelial cells, that one can identify inhibitors of angiogenesis" and points to the claims, abstract, and paragraph [0090] in support (Examiner's Answer, page 15). The only mention of angiogenesis in Mor is in paragraph [0090], which makes a conclusory assertion that compounds identified by the assays disclosed could be used as "anti-angiogenic drugs." Except for this single statement, Mor only discloses the effect of Axl on cell proliferation (*e.g.,* Mor, paragraphs [0036], [0174], and [0241]), which as discussed above, does not predictably correlate with angiogenesis. Similarly, O'Donnell *et al.* disclose the role of Axl in endothelial cell survival (O'Donnell *et al.,* page 1175, col. 1 to page 1176, col. 2, top) and only provide speculation regarding potential roles of Axl in other cellular processes. Furthermore, Gas6 is an agonist for other tyrosine kinase receptors (such as Sky and Mer), in addition to Axl (O'Donnell *et al.*, page 1174, col 2, second full paragraph and page 1178, col. 2, second paragraph), and its effects on endothelial cells are therefore not necessarily mediated by Axl. Thus, particularly in light of the teaching of Frater-Schroder *et al.*, one of skill in the art

would not have a reasonable expectation of success in identifying inhibitors of angiogenesis by screening for inhibitors of Axl, as in Appellants' claims.

Conclusion

Appellants submit that the rejection under 35 U.S.C. § 103 should be reversed, and respectfully request the allowance of the pending claims.

Respectfully submitted,

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